Human Sleep Neurophysiology

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Oscillatory events in the human sleep EEG - incidence and properties in baseline and recovery sleep after sleep deprivation

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Introduction: The human sleep EEG is characterised by the occurrence of distinct oscillatory events such as delta waves, sleep spindles, and alpha activity. Using a recently proposed algorithm for the detection of such events (1) we investigated their incidence, frequency and topographic distribution in baseline and recovery sleep after 40 h of prolonged wakefulness.

Methods: Sleep EEG data of eight healthy young males were analysed [baseline and recovery night; 27 derivations, extended 10–20 system; referenced to linked mastoid and average reference; sampling rate 128 Hz; for details see (2)]. Oscillatory events were detected using a method based on the estimation of autoregressive (AR) models on overlapping 1-s segments (1). Events were characterised by their frequency and duration and topographic differences of their properties were studied.

Results: The increase in spectral power in the delta and in the alpha band after sleep deprivation was correlated with the increased number of oscillatory events in these bands. The effect of sleep deprivation on alpha and sigma oscillations was more obvious in the event analysis than in the power spectra. A significant decrease in the number of sleep spindles after sleep deprivation was found in five subjects, no change in two subjects and an increase in one subject. The periodicity in the occurrence of oscillatory events was not affected by sleep deprivation. Preliminary results regarding the topographic distribution of events revealed a strong influence of the reference electrode (average reference versus linked mastoid).

Conclusion: The analysis of the sleep EEG by studying oscillatory events is a promising tool to develop a more detailed understanding of the processes underlying sleep regulation at the level of thalamocortical networks.

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TMS-evoked potentials during wakefulness, NREM and REM sleep

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In a previous study we used a combination of navigated transcranial magnetic stimulation (TMS) and high-density electroencephalography (HD-EEG) to measure the changes in cortical excitability and connectivity occurring during the progression from wakefulness to deep NREM sleep. These results suggested that a breakdown of cortical effective connectivity might be responsible for the fading of consciousness during NREM sleep early in the night. The aim of the present study is to test whether cortical effective connectivity recovers, at least in part, during late-night sleep, especially during REM sleep, a time at which conscious reports become longer and more vivid. Low frequency (< 1 Hz) TMS was delivered to premotor cortex while subjects (n = 10) lied on a reclining chair. An infrared positioning system and a 60-channel TMS-compatible EEG amplifier were used to target the cortical region of interest while recording TMS-evoked potentials over the entire scalp. Experiments were performed both early (12:00 PM) and late in the night (7:00 AM). All subjects progressed from wakefulness to NREM sleep while stimulation was delivered. Six subjects also entered a stable period of REM sleep. In all subjects, during wakefulness, TMS induced a sustained response made of recurrent waves of activity. Specifically, a sequence of time-locked high-frequency (20–35 Hz) oscillations occurred in the first 100 ms and was followed by a few slower components that persisted until 300 ms. During NREM sleep the initial fast oscillations were replaced by a high-amplitude, slower component and all TMS-evoked activity extinguished before 150 ms. With the onset of REM sleep, the high-frequency oscillations evoked by TMS were partially recovered. Source modeling analysis indicated that, during REM sleep, the propagation of TMS evoked activity was intermediate between wakefulness and NREM sleep. These results suggest that the level of cortical effective connectivity seems to fluctuate coherently with the level of consciousness across the sleep-wake cycle.

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Neural correlates of sleep spindles as revealed by simultaneous electroencephalography (EEG) and functional magnetic resonance imaging (FMRI)

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The present study aimed at identifying the neural correlates of spontaneous sleep spindle events using simultaneous EEG/FMRI recordings. Thalamic spindle generation and its synchronization by corticothalamic projections have been extensively studied in animals (1). While PET studies consistently revealed widespread deactivations during NREM sleep (2), on a cortical level various groups reported centroparietal spindle sources in humans using EEG (3) and MEG (4) techniques. 26 healthy young subjects were scanned during the first half of the night in a Siemens Allegra 3T scanner (Siemens, Erlangen, EPI sequence: 32 slices, voxel size: 3.4 × 3.4 × 3 mm, TR: 2460 ms, TE: 40 ms, FA: 90 °) with a full-montage of MR-compatible EEG electrodes attached. Subjects were not sleep-deprived and were monitored for regular sleep-wake cycles before acquisitions. After removing scanner and ballistocardiogram artifacts Cz sleep spindles were (i) automatically detected (5) for stage 2 and 3 of non-rapid eye movement (REM) sleep, (ii) visually checked and (iii) then entered as regressors of interest in FMRI analyses. The FMRI analysis (SPM5) used a mixed-effects model. At the individual level regional brain responses to spindles were modelled with the canonical basis set. Summary statistics images representing the main-effects of spindles were introduced in a random-effects ANOVA. Statistical inferences

were conducted at *P*SVC < 0.05. out of 26 subjects, 14 participants did have good signal quality for EEG spindle detection as well as sufficient (NREM) sleep to be further processed. Significant positive responses were identified in the thalamus, parahippocampal gyrus, cingulate cortex, insula, and superior temporal gyrus.

Results: This results demonstrate that an accurate neuroanatomical localization of transient events like spindles benefit from the combination of EEG and FMRI.

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Active brain processes during human quiescent sleep

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Introduction/Aim: At the cellular level in animals, the slow oscillation of non-REM sleep alternates phases of hyperpolarization and depolarization (1). The latter correspond to periods of intense neuronal firing. At the macroscopic level in humans, this implies that non-REM sleep cannot be solely reduced to a state of brain deactivation. Non-REM sleep might actually be related to regional brain activity in phase with the slow oscillation. Using simultaneous EEG/FMRI, this study aimed at characterizing the brain regional activity during non-REM sleep related to the depolarizing phases of slow oscillations.

Methods: Twenty-six non-sleep deprived, healthy, young subjects were scanned during the first half of the night in a 3T FMRI scanner (echoplanar sequence [EPI], 32 slices, TR = 2.46 s, TE = 40 ms, voxel size = $3.4 \times 3.4 \times 3$ mm^3), with a continuous 64-channels EEG recording. After scanner and pulse artifact removal, non-REM sleep (stages 2–4) epochs and corresponding FMRI time series were selected. Slow waves were automatically detected on EEG channels as in (2). The maximum negativity was taken as event of interest for each detected slow oscillation. The analysis was conducted in SPM5. We looked for the brain areas in which the BOLD signal was significantly correlated with the occurrence of these slow oscillations across subjects.

Results: Out of 26 subjects, 14 subjects slept and could be used for analyses. Significant positive brain responses correlated to slow oscillations were found in the brainstem, thalamus, cerebellum, limbic/paralimbic structures (parahippocampal gyrus, anterior cingulate cortex, insula), lateral inferior frontal gyrus and medial occipital cortex.

Conclusion: We found that, at the macroscopic level in normal humans, the brain remains active during non-REM sleep, in phase with the depolarizing part of the slow oscillation. This brain activity occurs in a distinct set of cortical and subcortical areas including structures known to be involved in non-REM sleep oscillations.

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Adenosine A1 receptor occupancy and sleep deprivation: a pet study

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Adenosine and adenosine receptors may play a role in human sleep regulation. The A1 receptor (A1AR) is highly expressed in brain regions involved in sleep. The non-selective adenosine A1 and A2A receptor antagonist, caffeine, stimulates alertness and attenuates sleep-deprivation induced changes in the waking and sleep EEG. The distinct roles of A1 and A2A receptors, however, for sleep regulation are controversial. The development of the selective A1AR antagonist 18F-CPFPX (Holschbach et al., 2002) offered the opportunity to visualize and quantify A1AR binding in the human brain. We combined positron emission tomography (PET) with 18F-CPFPX and quantitative EEG to determine whether A1AR occupancy is changed after prolonged waking (32 h awake) when compared to baseline (8 h awake). We also examined whether sleep-deprivation induced changes in A1AR binding and the EEG are attenuated by 300 mg slow-release caffeine. A caffeine group ($n = 5$) and a placebo group ($n = 5$) of young men completed the study. 18F-CPFPX accumulated in thalamus and cortex, while low ligand binding occurred in cerebellum and brain stem. The sleep-deprivation induced changes in A1AR occupancy were highly variable among individuals. In contrast, EEG theta (5–8 Hz) power, a proposed marker of sleep propensity in waking, increased during extended waking and this increase was attenuated by caffeine. The local differences in A1AR occupancy correspond to the reported density of A1AR in the brain. By determining the effects of sleep deprivation and caffeine on cerebral A1AR occupancy and the relationships to changes in the waking and sleep EEG, PET brain imaging with 18F-CPFPX may offer new insights into adenosinergic mechanisms of sleep regulation in humans.

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Laser evoked responses to painful stimulation during sleep

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Studies on the variation of awakening thresholds to cutaneous nociceptive stimuli demonstrate a gradation according to sleep depth comparable to that reported for auditory stimuli (Lavigne et al 00, Bentley et al 03). Conversely, while incorporation of auditory stimulation in dream content is frequent (Burton et al 1988), that of painful stimuli is seldom reported (Nielsen 93). The main objective of this work is to assess whether and how nociceptive information is processed during sleep in humans. We studied behavioural and electrophysiological responses to nociceptive stimuli during all-night sleep in 12 control subjects. Sequences of 10–30 thermal laser stimuli at pain threshold were delivered over the radial territory during all sleep stages. Subjects had no incorporation of painful stimuli and no recall of the stimuli on morning questionnaire. While trains of auditory stimuli 70 dB over perception level are seldom reported to arouse the

sleeping subjects (Bastuji et al 95, Perrin et al 99), thermal laser pulses less than 20 dB supra perceptive threshold had clear arousing properties. Even in cases where nociceptive stimulation did not interrupt sleep (awakening or arousal), it could trigger motor responses in up to 18% of trials. Contrary to previous reports suggesting an absence of cortical evoked potentials to laser (LEPs) during slow-wave sleep (Beydoun et al. 93, Qiu et al 02), we were able to record LEPs during all sleep stages. Sleep LEPs were attenuated and with unusual topography. During paradoxical sleep (PS) LEP components recorded over the frontal scalp virtually disappeared, while posterior components persisted. This is consistent with previously reported frontal metabolic deactivation during PS. The amplitude of a late LEP component (350–450 ms) was shown to predict the incoming arousal.

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Influence of bathing at different temperatures on sleep EEG power density spectra in healthy young women

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Correlational analyses have reported repercussions of core body temperature (CBT) on human sleep EEG spectra (e.g. J. Sleep Res. 1998, 7: 254–262). However, whether experimentally altered thermophysiological states affect sleep EEG power density in humans has not yet been examined. Therefore, we investigated the influence of different thermal interventions prior to sleep on thermoregulation and post-exposure sleep. Eight healthy young women (20–33 years, luteal menstrual phase) underwent three 35 min baths (warm 39 °C, neutral 35 °C and cold 28 °C) followed by a 2 h sleep episode on different days in randomized order under constant posture conditions throughout. These three different bath temperatures generated three different thermophysiological states of the body prior to sleep: heated up, indifferent and cooled down, with CBT of 37.49 °C, 37.24 °C, and 36.94 °C, respectively. The sleep EEG was recorded (Fz, Cz, Pz, Oz), visually scored and subjected to spectral analysis. In comparison to cool and neutral, warm bathing significantly changed EEG activity in the spindle and beta frequency range, such that EEG power density decreased in the low spindle (13.25–14.0 Hz) and increased in the high spindle frequency range (15–15.75 Hz). This led to significant changes in the log ratio of power density in the low to high frequency spindle range, particularly in the parietal derivation (Pz), reflected in a peak shift to higher frequencies in the spindle range. EEG beta activity was significantly reduced after the warm bath. Minor and non-consistent EEG differences were found between the cool and neutral baths. Our results indicate that it is rather the state of the thermoregulatory system (e.g. heat loss via distal vasodilation) that is crucial for changes in sleep EEG spectra than the level of CBT *per se*.

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Keywords: Temperature intervention, core body temperature, EEG spectral analysis

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Arousal events and NREM sleep dynamics

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Sequential spectral analysis data show that a typical NREM episode exhibits repeated alternations towards and away from deep sleep. While the neuronal transition probability (NTP) theory accounts for the unique relation between EEG spectral components during the dynamic states going-towards and going-away from deep sleep, it raises the question of the origin of these alternations. So far, spectral time-course dynamics have not been adequately related to the brief phasic arousal events that constitute a normal feature of sleep EEG. Here therefore we focus on the times of occurrence of the various types of these events and how they are related to the 'towards' and 'away' states. Data were obtained from 21 healthy subjects aged 20–30 years. For each subject, power spectra were computed by FFT over the range 0.5–30 Hz and the delta time-courses extracted. Each time-course for each NREM episode 1–4 was smoothed and divided into time intervals classified as either rising or falling delta. Arousal events were classified as either ASDA defined micro-arousals (MA), transient activation phases (TAP), bursts of K-complexes (KB) or bursts of delta waves (DB). A 2×4 contingency table was then constructed from these data and the chi-square statistic used to test independence between events and intervals. In all four NREM episodes there is a significant ($P < 0.0001$) association, with DB and KB events occurring mostly on the rising delta intervals, suggesting that they are synchronising type events. MA and TAP are already acknowledged to be desynchronising type events and as could be expected they occur mostly on the falling delta. It is a rather striking result that we see a clear one-to-one correlation between which one of the two types predominates and whether delta rises or falls.

Conclusion: Even without a statement of causality, our results are highly suggestive of the decisive effect of arousal type pre-dominance and this may be a key element in the establishment of the binary-state control of sleep dynamics inherent in the NTP model.

Keywords: Arousals, Delta power time-course, Neuronal transition probability model